REMARKS

In the Office action, claims 1-39 were considered. Claims 1-39 stand rejected. Applicant cancels claims 3, 10, 11, 19, 25, 26, 28-30, 38 and 39 without prejudice to subsequent reintroduction into this or a subsequently filed continuation application. Applicant amends claims 1, 4, 5, 8, 9, 12-14, 17, 18, 20, 23, 24, 31-33 and 36. Applicant submits no new matter is introduced by the amendments and that claims 1, 2, 4-9, 12-24, 27 and 31-37 are in condition for allowance.

Formal Drawings

Applicant submits herewith the formal drawings for this application.

Applicant submits that these formal drawings address the objections raised by the Official Draftsperson in Form PTO-948, a copy of which is attached.

Non-statutory Double Patenting Rejection

Applicant acknowledges that the non-statutory double patenting rejection is held in abeyance in this application.

Amendments to the Claims

Independent claims 1, 12, 20 and 31 are amended to recite administering a combination of an immunoconjugate including interleukin-2 and an angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin.

Dependent claims 4, 5, 8, 9, 13, 14, 17, 18, 23, 24, 32, and 33 are amended to correct their antecedent basis based on the amended independent claims.

Support for these amendments can be found in the specification as filed at least on page 5, lines 4-5; page 6, lines 4-6; page 10, line 27; page 17, line 29 to page 18, line 2; and originally filed claims 10, 11, 19, 25 and 26.

Applicant submits that no new matter is introduced by these amendments.

Rejections of Claims Under 35 U.S.C. § 112

Claim 3 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly is not described in the specification in a way to teach one skilled in the art to make and/or use the invention.

Without acquiescing to this rejection, Applicant cancels without prejudice claim 3, thus rendering this rejection moot.

Rejection of Claims Under 35 U.S.C. §103(a)

Claims 1-2 and 4-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al. (WO 92/08495) ("Gillies") in view of O'Reilly et al. (*Cell* 88: 277-285, 1997) ("O'Reilly I").

Claims 1, 11, and 26 are rejected as being unpatentable over Gillies in view of O'Reilly et al. (*Cell* 79: 315-328, 1994) ("O'Reilly II") or Brooks et al. (*Cell* 79: 1157-1164, 1994) ("Brooks") or Ingber et al. (*Nature* 348: 555-557, 1990) ("Ingber").

Without acquiescing to these rejections, Applicant submits that none of Gillies, O'Reilly I, O'Reilly II, Brooks or Ingber teaches or suggests the limitations of amended independent claims 1, 12, 20, and 31. That is, amended claims 1, 12, 20, and 31 recite administering an immunoconjugate that includes interleukin-2 in combination with an angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin. Because none of the cited references provides the necessary motivation to practice the specifically claimed invention, Applicant respectfully requests reconsideration and withdrawal of these rejections.

Further, Applicant submits that the claimed method demonstrates an unexpected property with respect to an effect on tumor growth. See Lode et al. (*Proc. Natl. Acad. Sci. USA* 96: 1591-1596, 1999) (attached as Exhibit A). Applicant submits that Lode reports an unexpected "[s]ynergy between an antiangiogenic integrin α_v antagonist and an antibody-cytokine fusion protein." For example, the abstract in Lode reports that "simultaneous treatments with the integrin α_v antagonist and tumor-specific antibody-IL-2 fusion proteins induced dramatic primary tumor regressions.... However, each agent used as monotherapy induced only a delay in tumor growth." Accordingly, the results of administering the claimed combination are unexpected in view of the knowledge in the art at the time of the invention. Therefore, Applicant submits that independent claims 1, 12, 20, and 31, and the claims depending therefrom, are unobvious over the cited references and respectfully requests that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

Applicant submits that on the basis of the foregoing remarks and claim amendments, claims 1, 2, 4-9, 12-24, 27, and 31-37 are in condition for immediate allowance. Accordingly, Applicant respectfully requests entry as such. The Examiner is respectfully requested to call the undersigned at (617) 248-7240 prior to issuing a further Office action in this application, if necessary.

Respectfully submitted,

Pat RH Vall

Patrick R.H. Waller, Ph.D.
Attorney for the Applicant
Reg. No. 41, 418

Date: June 6, 2002
Testa, Hurwitz & Thibeault
125 High Street
Boston, MA 02110
(617) 248-7240

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MARKED-UP VERSION OF AMENDEDCLAIMS SHOWING AMENDMENTS

1. (Twice Amended) A method of inducing a cytocidal immune response against a target cell [,] in a mammal, the method comprising:

administering to a mammal a combination of (i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a target cell and [a cytokine] interleukin 2, and (ii) an angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin,

wherein the combination induces a cytocidal immune response against the target cell that is greater than a response induced by the immunoconjugate alone.

4. (Amended) The method of claim 1, wherein the angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin is co-administered together with the immunoconjugate.

5. (Amended) The method of claim 1, wherein the angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin is administered prior to the immunoconjugate.

8. (Twice Amended) The method of claim 1, wherein the immunoconjugate is a fusion protein comprising, in an amino-terminal to carboxy-terminal direction, (i) the antibody binding site comprising an immunoglobulin variable region capable of binding a target antigen expressed on a target cell, an immunoglobulin CH1 domain, an immunoglobulin CH2 domain, and (ii) [the cytokine] interleukin 2.

9. (Amended) The method of claim 8, wherein the antibody binding site further comprises a CH3 domain interposed between the CH2 domain and [the cytokine] interleukin-2.

12. (Twice Amended) A method of inducing a cytocidal immune response against a cancer cell in a mammal, the method comprising:

administering to a mammal a combination of (i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a cancer cell and [a cytokine] interleukin-2, and (ii) an angiogenesis inhibitor [selected from the group consisting of endostatin and angiostatin] having binding affinity for $\alpha_v\beta_3$ integrin,

wherein the combination induces a cytocidal immune response against the cancer cell that is greater than a response induced by the immunoconjugate alone.

13. (Amended) The method of claim 12, wherein the angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin is co-administered together with the immunoconjugate.

14. (Amended) The method of claim 12, wherein the angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin is administered prior to the immunoconjugate.

17. (Twice Amended) The method of claim 12, wherein the immunoconjugate is a fusion protein comprising, in an amino-terminal to carboxy-terminal direction, (i) the antibody binding site comprising an immunoglobulin variable region capable of binding a target antigen expressed on a target cell, an immunoglobulin CH1 domain, an immunoglobulin CH2 domain, and (ii) [the cytokine] interleukin-2.

18. (Amended) The method of claim 17, wherein the antibody binding site further comprises a CH3 domain interposed between the CH2 domain and [the cytokine] interleukin-2.

20. (Twice Amended) A composition for inducing an immune response against a target cell in a mammal, the composition comprising in combination:

(i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a target cell and [a cytokine] interleukin-2, and (ii) an angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin,

wherein the combination induces a cytocidal immune response against the target cell that is greater than a response induced by the immunoconjugate alone.

23. (Twice Amended) The composition of claim 20, wherein the immunoconjugate is a fusion protein comprising, in an amino-terminal to carboxy-terminal direction, (i) the antibody binding site comprising an immunoglobulin variable region capable of binding a target antigen expressed on a target cell, an immunoglobulin CH1 domain, an immunoglobulin CH2 domain, and (ii) [the cytokine] interleukin-2.

24. (Amended) The composition of claim 23, wherein the antibody binding site further comprises a CH3 domain between the CH2 domain and [the cytokine] interleukin-2.

31. (Twice Amended) A method for reducing the size of a tumor in a mammal, the method comprising:

administering to a mammal (i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a target cell in a tumor and [a cytokine] interleukin-2, and (ii) an angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin,

wherein the combination induces a reduction in size of the tumor that is greater than a reduction in size induced by the immunoconjugate alone.

32. (Amended) The method of claim 31, wherein the angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin is co-administered together with the immunoconjugate.

33. (Amended) The method of claim 31, wherein the angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin is administered prior to the immunoconjugate.

36. (Twice Amended) The method of claim 31, wherein the immunoconjugate is a fusion protein comprising, in an amino-terminal to carboxy-terminal direction, (i) the antibody binding site comprising an immunoglobulin variable region capable of binding a target antigen expressed on a target cell, an immunoglobulin CH2 domain, and (ii) [the cytokine] interleukin-2.